UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/441,355	05/15/95	HOUGHTON	M 0063.021

EXAMINER	
ZEMAN, M	
ART UNIT	PAPER NUMBER
1815	3

18M1/1029

ALISA A HARBIN
CHIRON CORPORATION
INTELLECTUAL PROPERTY R440
PO BOX 8097
EMERYVILLE CA 94662-8097

DATE MAILED: 10/29/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 5/15/95

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 20, 32, 38+39 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 20, 32, 38+39 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

DETAILED ACTION

1. Claims 40-87 are pending in this application. Claims 20, 32, 28, and 39 were canceled by the amendment filed 5/5/97.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's arguments filed 5/5/97 have been fully considered but they are not completely persuasive.

4. In view of the cancellation of claims 20, 32, 38, and 39 the following rejections are withdrawn:

The rejections of claims 20, 32, 38, and 39 under 35 U.S.C. 112, second paragraph, are withdrawn in view of the cancellation of those claims.

The rejections of claims 32, 38 and 39 under 35 U.S.C. 102(b) as being clearly anticipated by any of Wands, Tabor, Tabor, Coursaget or Wands and under 35 U.S.C. 102(e) as being anticipated by any of Seto, Wands or Pillot are withdrawn.

The rejection of claim 20 under 35 U.S.C. 103(a) as being unpatentable over Valenzuela in view of Seto is withdrawn.

Claim Rejections - 35 USC § 112

5. Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 is drawn to immunogenic polypeptides wherein the sequence is derived from either strand of the cDNA sequences cloned and deposited with the ATCC. It is not clear how amino acid sequences derived from reading an HCV cDNA on the non-coding strand would produce any HCV specific and immunoreactive peptides. HCV is not known to contain any such open reading frames, nor is there indication of any non-coding strand open reading frames in the instant application. One would not expect peptides derived from non-coding strand sequences to specifically immunoreact with antibodies to HCV, nor would one expect those same peptides to induce a specific anti-HCV response upon immunization of a subject.

6. Claims 40-87 are again rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the previous office action.

Claims 40-87 each recite an immunogenic polypeptide, or depend from a claim reciting an immunogenic polypeptide. As discussed above, an immunogenic polypeptide is capable of eliciting a specific immune response in the immunized individual. An immunogen does not necessarily produce protective immunity.

An immunogenic polypeptide is setforth in the specification as being "a polypeptide that elicits a cellular and/or humoral immune response, whether alone or linked to a carrier in the presence or absence of an adjuvant." Immunological responses would include antibodies that bind specific regions or epitopes of that immunogenic polypeptide. The specification defines HCV epitopes in two ways: as an antigenic determinant of a polypeptide, and as an immunologically identifiable sequence unique to HCV. The specification does not teach how to identify peptides would be immunogenic, and would have a reasonable expectation of not being cross-reactive with other flaviviruses, from examining the nucleic acid or amino acid sequences disclosed in this application. In order to identify such a sequence, one must have a method of predicting which sequences would a) contain an epitope, and b) be specific only for HCV and not for other flaviviruses. Such methods are unknown in the art. The Hopp reference (Hopp, 1981) discloses computer algorithms for identifying regions of an amino acid sequence likely to be antigenic, or immunoreactive, with an antibody based upon regions of hydrophobicity. These methods do not speak to the immunospecificity of the antibodies that would bind to these regions, nor does Hopp speak to the specificity of an immune system response to a peptide comprising the predicted sequence. Hopp does not at all speak to the immunogenicity of such a peptide. Even using the methods of Hopp, there is no way to predict which amino acids in a predicted sequence are critical for the antigenicity of the epitope and which amino acids merely provide the framework or scaffolding for the epitopic site. This information cannot be gotten through comparisons of sequence similarities with other flaviviruses. Methods suggested in the

specification for determining spatial conformations of HCV polypeptides are x-ray crystallography and 2D-NMR. Such methods do not lend themselves to screening of upwards of 9000 polypeptides encompassed by the pending claims. There is no direction in the specification indicating which elements of a particular sequence would fold properly to present HCV epitopes, or how that knowedge would be derived from the x-ray crystallographs or NMR spectra.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 40-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Bradley.

Claims 40-51 are drawn to immunogenic, purified HCV polypeptides, comprising at least 8 contiguous amino acids of various sequences found within the figures or the deposits to the ATCC.

Bradley (Bradley 1985 J Virological Methods 10 p307-319) discloses several purified or isolated NANBV agents, which are infectious, and produce NANBH in chimpanzees. One is a concentrated fraction of Factor VIII, both unpassaged, and passaged twice through chimpanzees. Bradley also discusses the "F" strain and the "H" strain, both isolated by Feinstone, and infectious. The "H" strain was later identified as HCV, and is also variously called the

Hutchinson strain (see Ogata et al. 1991 PNAS USA 88 p 3392-3396). All of these viral preparations comprise at least 8 amino acids of HCV sequence, and provoke an immune response.

9. Claims 40-51 are rejected under 35 U.S.C. 102(b) as being anticipated by He.

He (He et al. 1987 J Infectious Diseases 136 (4) p 636) discloses purified preparations of the "H" strain of HCV, also known as the Hutchinson strain. He sizes the H strain virions through filtration. The filtered virus was still infectious. He indicates that flaviviruses are among the types of viruses that would be of the size collected in the infectious filtered sample. This purified fraction comprises a polypeptide having at least 8 contiguous amino acids of HCV, and is able to provoke an immune response unpon immunization, or infection with that fraction.

10. Claims 40-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Prince.

Prince (Prince et al. J Medical Virology 16 p119-125) discloses a method of inactivating the Hutchinson strain of HCV. One sample of the Hutchinson strain is sterilized by treatment with beta-propiolactone and UV light. The treated sample was non-infectious. The untreated sample was infectious. This control inoculum of the Hutchinson strain of HCV comprises an immunogenic HCV polypeptide having at least 8 nucleotides of an HCV sequence.

Conclusion

11. No claim is allowed.

12. The following suggestions concerning the wording of the pending claims would further clarify the claimed invention:

In claim 43, (43-46, 55-58) language that would more clearly identify the claimed sequences could be: "...sequence is encoded by a nucleotide sequence within Figure 14."

Similarly in claim 53: "sequence is encoded by a nucleotide sequence of the C domain of HCV"

Claim 54: "sequence is encoded by a nucleotide sequence of the envelope..."

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

14. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37

CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $750 for a large entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. If a notice of appeal and the appeal fee set forth in 37 CFR 1.17(e) were filed prior to or with the payment of the fee set forth in 37 CFR 1.17(r), the payment of the fee set forth in 37 CFR 1.17(r) by applicant will be construed as a request to dismiss the appeal and to continue prosecution under 37 CFR 1.129(a). In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 8:00 am and 5:30 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

The fax number for this Art Unit is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
August 11, 1997

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800